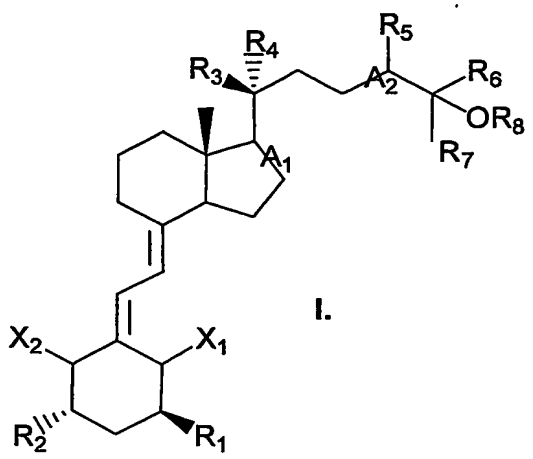
CLAIMS

1. A vitamin D_3 compound of formula I:



I.

wherein:

A_1 is single or double bond;

A_2 is a single, double or triple bond;

X_1 and X_2 are each independently H_2 or $=CH_2$, provided X_1 and X_2 are not both $=CH_2$;

R_1 and R_2 are each independently $OC(O)C_1$-C_4 alkyl, OC(O)hydroxyalkyl, or OC(O)haloalkyl;

R_3, R_4 and R_5 are each independently hydrogen, C_1-C_4 alkyl, hydroxyalkyl, or haloalkyl, with the understanding that R_5 is absent when A_2 is a triple bond, or R_3 and R_4 taken together with C_{20} form C_3-C_6 cycloalkyl;

R_6 and R_7 are each independently alkyl or haloalkyl; and

R_8 is H, $C(O)C_1$-C_4 alkyl, C(O)hydroxyalkyl, or C(O)haloalkyl;

provided that when A_1 is single bond, R_3 is hydrogen and R_4 is methyl, then A_2 is a double or triple bond; and

pharmaceutically acceptable esters, salts, and prodrugs thereof.

2. The compound of claim 1, wherein X_1 is H_2 and X_2 is $=CH_2$.

3. The compound of claim 1, wherein X_1 and X_2 are H_2.

4. The compound of any preceding claim, wherein A_1 is a single bond.

5. The compound of any preceding claim, wherein A_1 is a double bond.

6. The compound of any preceding claim, wherein A_2 is a single bond.

7. The compound of any preceding claim, wherein A_2 is a double bond.

8. The compound of any preceding claim, wherein A_2 is triple bond.

9. The compound of any preceding claim, wherein R_3 is hydrogen.

10. The compound of any preceding claim, wherein R_4 is C_1-C_4 alkyl.

11. The compound of any preceding claim, wherein R_3 and R_4, taken together with C_{20}, form C_3-C_6 cycloalkyl.

12. The compound of any preceding claim, wherein R_3 and R_4, taken together with C_{20}, form cyclopropyl.

13. The compound of any preceding claim, wherein R_1 and R_2 are each independently $OC(O)C_1$-C_4 alkyl.

14. The compound of any preceding claim, wherein R_1 and R_2 are each $OC(O)CH_3$.

15. The compound of any preceding claim, wherein R_6 and R_7 are each independently alkyl or haloalkyl.

16. The compound of any predecing claim, wherein R_6 and R_7 are each independently methyl or trifluoromethyl.

17. The compound of any predecing claim, wherein R_6 and R_7 are each methyl.

18. The compound of any predecing claim, wherein R_6 and R_7 are each ethyl.

19. The compound of any preceding claim, wherein R_6 and R_7 are each trifluoromethyl.

20. The compound of claim 9, wherein R_6 is methyl and R_7 is trifluoromethyl.

21. The compound of any preceding claim, wherein R_8 is H or $C(O)C_1$-C_4 alkyl.

22. The compound of any preceding claim, wherein R_8 is H.

23. The compound of any preceding claim, wherein R_8 is $C(O)CH_3$.

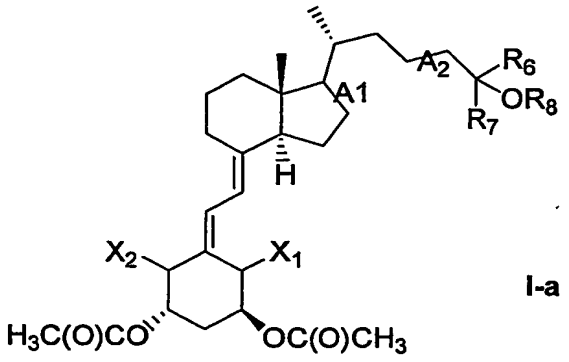
24. The compound of claim 4, wherein A_2 is a double bond.

25. The compound of claim 4, wherein A_2 is a triple bond.

26. The compound of any of claims 24-25, wherein R_3 is H and R_4 is C_1-C_4 alkyl.

27. The compound of any of claims 24-26, wherein R_4 is methyl.

28. The compound of claim 1 having formula I-a



I-a

29. The compound of claim 28, wherein X_1 is $=CH_2$ and X_2 is H_2.

30. The compound of claim 28, wherein X_1 and X_2 are each H_2.

31. The compound of any of claims 28-30, wherein A_1 is a double bond.

32. The compound of any of claims 28-31, wherein A_2 is a single bond.

33. The compound of any of claims 28-31, wherein A_2 is a double bond.

34. The compound of any of claims 28-31, wherein A_2 is triple bond.

35. The compound of any of claims 28-30, wherein A_1 is a single bond and A_2 is a double bond.

36. The compound of any of claims 28-30, wherein A_1 is a single bond and A_2 is a triple bond.

37. The compound of any of claims 28-36, wherein R_8 is H or $C(O)CH_3$.

38. The compound of any of claims 28-37, wherein R_6 and R_7 are alkyl.

39. The compound of any preceding claim 28-38, wherein R_6 and R_7 are methyl.

40. The compound of any of claims 28-38, wherein R_6 and R_7 are ethyl.

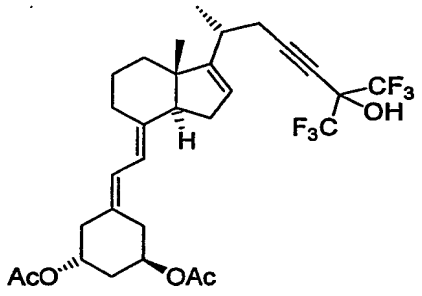
41. The compound of any of claims 28-37, wherein R_6 and R_7 are haloalkyl.

42. The compound of claim 41, wherein R_6 and R_7 are trifluoroalkyl.

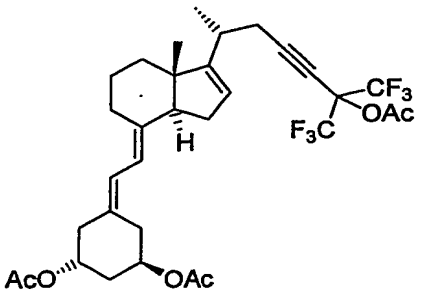
43. The compound of claim 41 or 42, wherein R_6 and R_7 are trifluoromethyl.

44. The compound of any of claims 28-37, wherein R_6 is trifluoromethyl and R_7 is methyl.

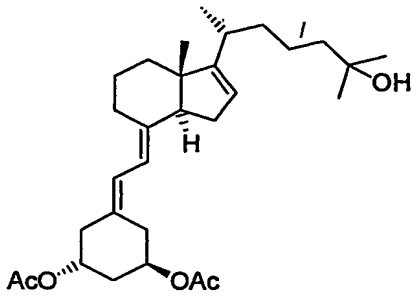
45. The compound of claim 28, wherein said compound is 1,3-Di-O-acetyl-1,25-Dihydroxy-16-ene-23-yne-26,27-hexafluoro-19-nor-cholecalciferol:



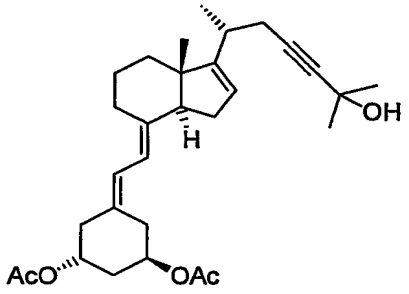
46. The compound of claim 28, wherein said compound is 1,3,25-Tri-O-acetyl-1,25-Dihydroxy-16-ene-23-yne-26,27-hexafluoro-19-nor-cholecalciferol:



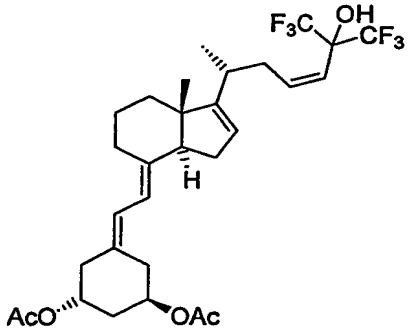
47. The compound of claim 28, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-16-ene-19-nor-cholecalciferol:



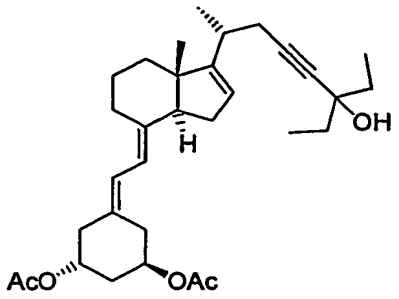
48. The compound of claim 28, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-16-ene-23-yne-19-nor-cholecalciferol:



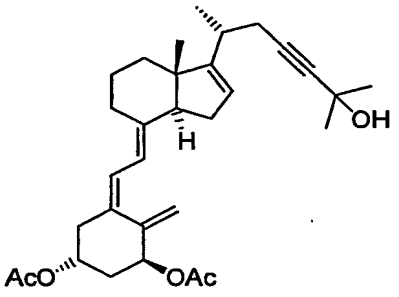
49. The compound of claim 28, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-16,23Z-diene-26,27-hexafluoro-19-nor-cholecalciferol:



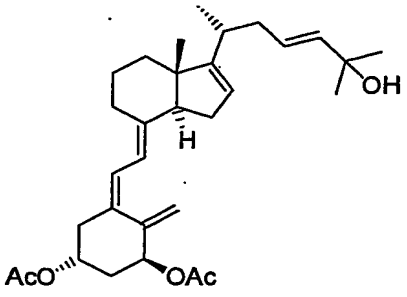
50. The compound of claim 28, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-16-ene-23-yne-26,27-bishomo-19-nor-cholecalciferol:



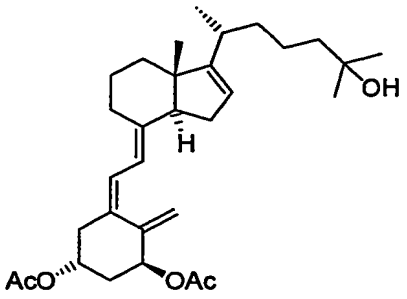
51. The compound of claim 28, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-16-ene-23-yne-cholecalciferol:



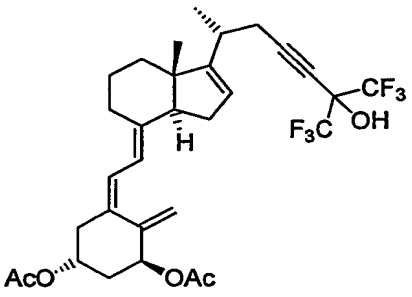
52. The compound of claim 28, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-16,23E-diene-cholecalciferol:



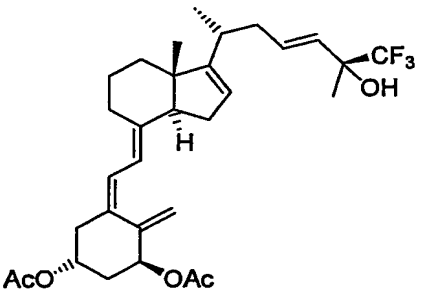
53. The compound of claim 28, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-16-ene-cholecalciferol:



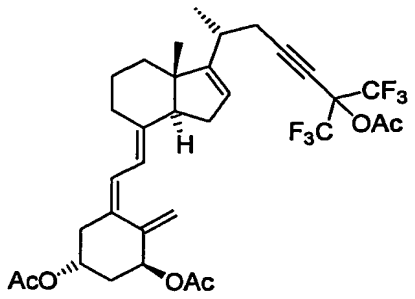
54. The compound of claim 28, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-16-ene-23-yne-26,27-hexafluoro-cholecalciferol:



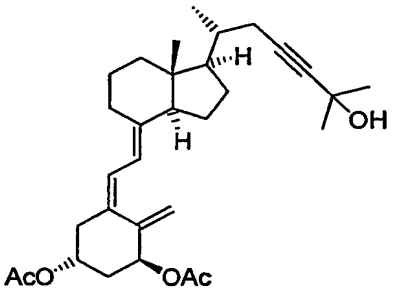
55. The compound of claim 1, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-16,23E-diene-25R-26-trifluoro-cholecalciferol:



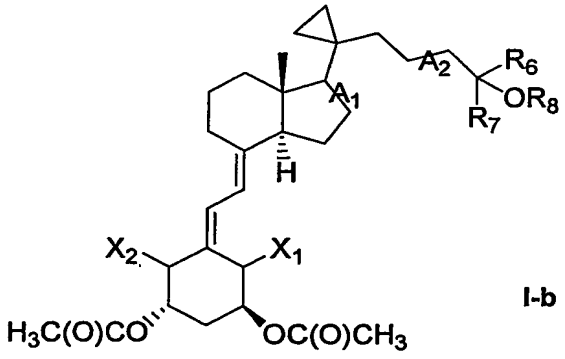
56. The compound of claim 28, wherein said compound is 1,3,25-Tri-O-acetyl-1,25-dihydroxy-16-ene-23-yne-26,27-hexafluoro-cholecalciferol:



57. The compound of claim 28, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-23-yne-cholecalciferol:



58. The compound of claim 1having formula I-b



I-b

59. The compound of claim 58, wherein A_1 is a single bond.

60. The compound of claim 58, wherein A_1 is a double bond.

61. The compound of any claims 58-60, wherein and A_2 is a single bond.

62. The compound of any claims 58-60, wherein A_2 is double bond.

63. The compound of any of claims 58-60, wherein A_2 is a triple bond.

64. The compound of any of claims 58-63, wherein X_1 is $=CH_2$ and X_2 is H.

65. The compound of claims 58-63, wherein X_1 and X_2 are each H.

66. The compound of any of claims 58-65, wherein R_8 is H or $C(O)CH_3$.

67. The compound of any of claims 58-65 wherein R_8 is H.

68. The compound of any of claims 58-67, wherein R_6 and R_7 are alkyl.

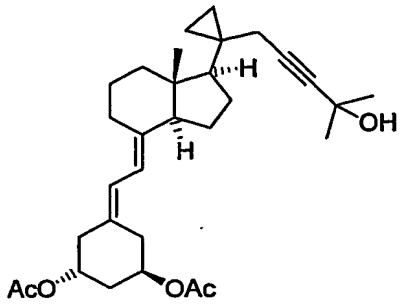
69. The compound of any of claims 58-67, wherein R_6 and R_7 are methyl.

70. The compound of any of claims 58-67, wherein R_6 and R_7 are haloalkyl.

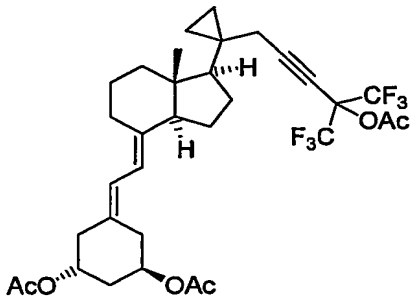
71. The compound of any of claims 58-67, wherein R_6 and R_7 are trifluoroalkyl.

72. The compound of any of claims 58-67, wherein R_6 and R_7 are trifluoromethyl.

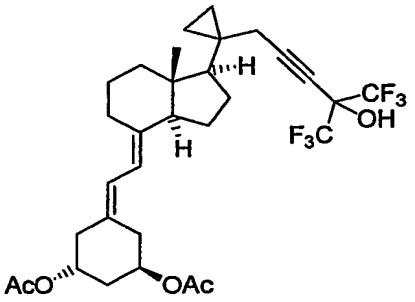
73. The compound of claim 58, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-20-cyclopropyl-23-yne-19-nor-cholecalciferol:



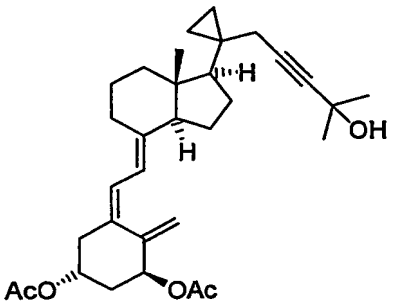
74. The compound of claim 58, wherein said compound is 1,3,25-Tri-O-acetyl-1,25-dihydroxy-20-cyclopropyl-23-yne-26,27-hexafluoro-19-nor-cholecalciferol:



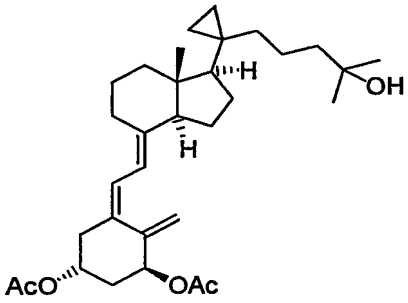
75. The compound of claim 58, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-20-cyclopropyl-23-yne-26,27-hexafluoro-19-nor-cholecalciferol:



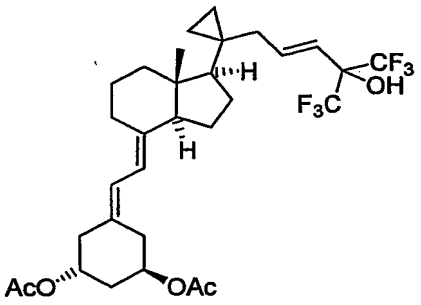
76. The compound of claim 58, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-20-cyclopropyl-23-yne-cholecalciferol:



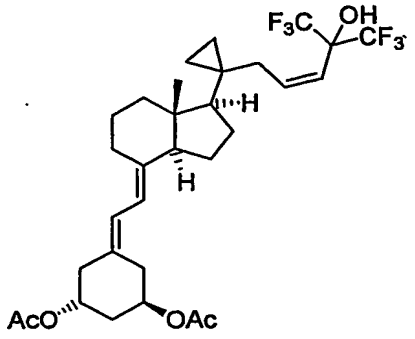
77. The compound of claim 58, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-20-cyclopropyl-cholecalciferol:



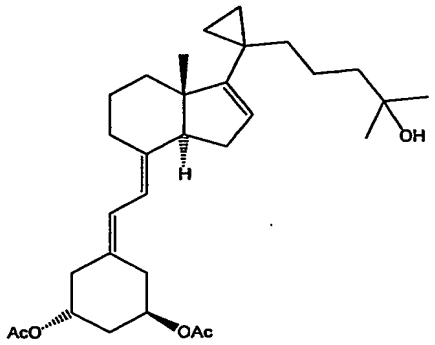
78. The compound of claim 58, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-20-cyclopropyl-23E-ene-26,27-hexafluoro-19-nor-cholecalciferol:



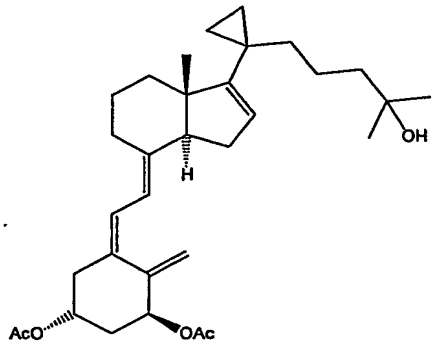
79. The compound of claim 58, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-20-cyclopropyl-23Z-ene-26,27-hexafluoro-19-nor-cholecalciferol:



80. The compound of claim 58, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-16-ene-20-cyclopropyl-19-nor-cholecalciferol:



81. The compound of claim 58, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-16-ene-20-cyclopropyl-cholecalciferol:



82. A method for treating a subject for a vitamin D_3 associated state, comprising administering to said subject in need thereof an effective amount of a

vitamin D_3 compound of any one of claims 1-81, such that said subject is treated for said vitamin D_3 associated state.

83. The method of claim 82, wherein said vitamin D_3 associated state is an ILT3-associated disorder.

84. The method of claim 83, wherein said ILT3-associated disorder is an immune disorder.

85. The method of claim 84, wherein said immune disorder is an autoimmune disorder.

86. The method of claim 85, wherein said autoimmune disorder is selected from the group consisting of type 1 insulin-dependent diabetes mellitus, adult respiratory distress syndrome, inflammatory bowel disease, dermatitis, meningitis, thrombotic thrombocytopenic purpura, Sjogren's syndrome, encephalitis, uveitis, uveoretinitis, leukocyte adhesion deficiency, rheumatoid arthritis, rheumatic fever, Reiter's syndrome, psoriatic arthritis, progressive systemic sclerosis, primary biliary cirrhosis, pemphigus, pemphigoid, necrotizing vasculitis, myasthenia gravis, multiple sclerosis, lupus erythematosus, polymyositis, sarcoidosis, granulomatosis, vasculitis, pernicious anemia, CNS inflammatory disorder, antigen-antibody complex mediated diseases, autoimmune haemolytic anemia, Hashimoto's thyroiditis, Graves disease, habitual spontaneous abortions, Reynard's syndrome, glomerulonephritis, dermatomyositis, chronic active hepatitis, celiac disease, autoimmune complications of AIDS, atrophic gastritis, ankylosing spondylitis and Addison's disease.

87. The method of claim 84, wherein said immune disorder is transplant rejection.

88. The method of claim 86, wherein said autoimmune disorder is type I insulin dependent diabetes mellitus.

89. The method of claim 82, wherein said vitamin D_3 associated state is a disorder characterized by an aberrant activity of a vitamin D_3-responsive cell.

90. The method of claim 89, wherein said disorder comprises an aberrant activity of a hyperproliferative skin cell.

91. The method of claim 90, wherein said disorder is selected from psoriasis, basal cell carcinoma and keratosis.

92. The method of claim 89, wherein said disorder comprises an aberrant activity of an endocrine cell.

93. The method of claim 92, wherein said endocrine cell is a parathyroid cell and the aberrant activity is processing and/or secretion of parathyroid hormone.

94. The method of claim 93, wherein said disorder is secondary hyperparathyroidism.

95. The method of claim 89, wherein said disorder comprises an aberrant activity of a bone cell.

96. The method of claim 95, wherein said disorder is selected from osteoporosis, osteodystrophy, senile osteoporosis, osteomalacia, rickets, osteitis fibrosa cystica, and renal osteodystrophy.

97. The method of claim 89, wherein said disorder is cirrhosis or chronic renal disease.

98. The method of claim 82, wherein said vitamin D_3 compound is administered in combination with a pharmaceutically acceptable carrier.

99. A method of ameliorating a deregulation of calcium and phosphate metabolism, comprising administering to a subject a therapeutically effective amount of a compound of any one of claims 1 to 81, so as to ameliorate the deregulation of the calcium and phosphate metabolism.

100. The method of claim 99, wherein the deregulation of the calcium and phosphate metabolism leads to osteoporosis.

101. A method of modulating the expression of an immunoglobulin-like transcript 3 (ILT3) surface molecule in a cell, comprising contacting said cell with a compound of any one of claims 1-81 in an amount effective to modulate the expression of an immunoglobulin-like transcript 3 (ILT3) surface molecule in said cell.

102. The method of claim 101, wherein said cell is within a subject.

103. A method of treating an ILT3-associated disorder in a subject, comprising administering to said subject a compound of any one of claims 1-81 in an amount effective to modulate the expression of an ILT3 surface molecule, thereby treating said ILT3-associated disorder in said subject.

104. The method of claim 103, wherein said ILT3-associated disorder is an immune disorder.

105. The method of claim 104, wherein said immune disorder is an autoimmune disorder.

106. The method of claim 105, wherein said autoimmune disorder is type insulin dependent diabetes mellitus.

107. A method of inducing immunological tolerance in a subject, comprising administering to said subject a compound of any one of claims 1-81 in an amount effective to modulate the expression of an ILT3 surface molecule, thereby inducing immunological tolerance in said subject.

108. The method of claim 107, wherein said immunological tolerance is induced in an antigen-presenting cell.

109. The method of claim 108, wherein said antigen-presenting cell is selected from the group consisting of dendritic cells, monocytes, and macrophages.

110. A method of inhibiting transplant rejection in a subject comprising administering to said subject a compound of any one of claims 1-81 in an amount effective to modulate the expression of an ILT3 surface molecule, thereby inhibiting transplant rejection in said subject.

111. The method of claim 110, wherein said transplant is a solid organ transplant.

112. The method of claim 110, wherein said transplant is a pancreatic islet transplant.

113. The method of claim 110, wherein said transplant is a bone marrow transplant.

114. The method of any one of claims 99, 101, 103, 107, or 110, wherein said vitamin D_3 compound is administered to the subject using a pharmaceutically-acceptable formulation.

115. The method of claim 114, wherein said pharmaceutically-acceptable formulation provides sustained delivery of said vitamin D_3 compound to a subject for at least four weeks after the pharmaceutically-acceptable formulation is administered to the subject.

116. A method for modulating immunosuppressive activity by an antigen-presenting cell, comprising contacting an antigen-presenting cell with a compound of any one of claims 1-81 in an amount effective to modulate ILT3 surface molecule expression, thereby modulating said immunosuppressive activity by said antigen-presenting cell.

117. The method of any one of claims 99, 101, 103, 107, or 110, wherein said subject is a mammal.

118. The method of claims 101 or 116, wherein said cell is an antigen-presenting cell.

119. The method of claim 118, wherein said antigen-presenting cell is selected from the group consisting of dendritic cells, monocytes, and macrophages.

120. The method of any one of claims 101, 103, 107, or 110, wherein the expression of said immunoglobulin-like transcript 3 (ILT3) surface molecule is upregulated.

121. The method of any one of claims 82, 99, 101, 103, 107, or 110, wherein said compound is administered orally.

122. The method of any one of claims 82, 99, 101, 103, 107, or 110,wherein said compound is administered intravenously.

123. The method of any one of claims 82, 99, 101, 103, 107, or 110, wherein said compound is administered topically

124. The method of any one of claims 82, 99, 101, 103, 107, or 110, wherein compound is administered parenterally.

125. The method of any one of claims 82, 99, 101, 103, 107, or 110, wherein said compound is administered at a concentration of 0.001 μg – 100 μg/kg of body weight.

126. The method of claim 125, wherein said compound is 1,3-Di-O-acetyl-1,25-dihydroxy-16,23Z-diene-26,27-hexafluoro-19-nor-cholecalciferol (2).

127. The method of claim 125, wherein said compound is 1,3-Di-O-acetyl-1,25-Dihydroxy-16-ene-23-yne-26,27-hexafluoro-19-nor-cholecalciferol (4).

128. The method of claim 125, wherein said compound is 1,3,25-Tri-O-acetyl-1,25-Dihydroxy-16-ene-23-yne-26,27-hexafluoro-19-nor-cholecalciferol (5).

129. The method of claim 89, wherein the disorder is hypertension.

130. The method of claim 129, wherein the compound suppresses expression of renin, thereby treating the subject for hypertension.

131. The method of claim 89, wherein the disorder is benign prostate hypertrophy.

132. The method of claim 89, wherein the disorder is neoplastic disease.

133. The method of claim 132, wherein the neoplastic disease is selected from the group consisting of leukemia, lymphoma, melanoma, osteosarcoma, colon cancer, rectal cancer, prostate cancer, bladder cancer, and malignant tumors of the lung, breast, gastrointestinal tract, and genitourinary tract.

134. The method of claim 133, wherein the neoplastic disease is bladder cancer.

135. The method of claim 89, wherein the disorder is neuronal loss.

136. The method of claim 135, wherein the disorder is selected from the group consisting of Alzheimer's Disease, Pick's Disease, Parkinson's Disease, Vascular Disease, Huntington's Disease, and Age-Associated Memory Impairment.

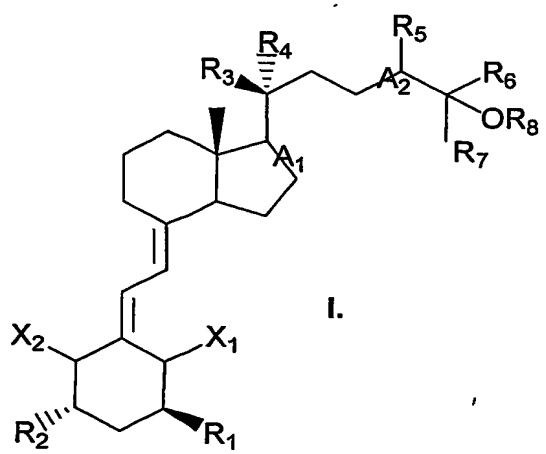
137. The method of claim 89, wherein the disorder is characterized by an aberrant activity of a vitamin D_3-responsive smooth muscle cell.

138. The method of claim 137, wherein the disorder is hyperproliferative vascular disease selected from the group consisting of hypertension-induced vascular remodeling, vascular restenosis, and atherosclerosis.

139. The method of claim 137, wherein the disorder is arterial hypertension.

140. A method for preventing or treating bladder dysfunction in a subject in need thereof by administering an effective amount of a compound of any of claims 1-81 thereby to prevent or treat bladder dysfunction in said subject.

141. A method for preventing or treating bladder dysfunction in a subject in need thereof by administering an effective amount of a compound of formula I:



I.

wherein:

A_1 is single or double bond;

A_2 is a single, double or triple bond;

X_1 and X_2 are each independently H_2 or $=CH_2$, provided X_1 and X_2 are not both $=CH_2$;

R_1 and R_2 are each independently $OC(O)C_1$-C_4 alkyl, OC(O)hydroxyalkyl, or OC(O)haloalkyl;

R_3, R_4 and R_5 are each independently hydrogen, C_1-C_4 alkyl, hydroxyalkyl, or haloalkyl, with the understanding that R_5 is absent when A_2 is a triple bond, or R_3 and R_4 taken together with C_{20} form C_3-C_6 cycloalkyl;

R_6 and R_7 are each independently alkyl or haloalkyl; and

R_8 is H, $C(O)C_1$-C_4 alkyl, C(O)hydroxyalkyl, or C(O)haloalkyl; and

pharmaceutically acceptable esters, salts, and prodrugs thereof;
thereby to prevent or treat bladder dysfunction in said subject.

142. The method of claim 140 or 141 wherein the compound is formulated in a pharmaceutical composition together with a pharmaceutically acceptable diluent or carrier.

143. The method of any one of claims 140 -142, wherein said compound is a Vitamin D receptor agonist.

144. The method of any one of claims 140-143, wherein said bladder dysfunction is characterized by the presence of bladder hypertrophy.

145. The method of any one of claims 140-144, wherein said bladder dysfunction is overactive bladder.

146. The method of any one of claims 140-145 , wherein the subject is male.

147. The method of claim 140-146, wherein the male concurrently suffering from BPH.

148. The method of any one of claims 140-147, wherein the subject is female.

149. The method of any of claims 82-147, wherein the subject is a mammal.

150. The method of any of claims 82-149, wherein the subject is human.

151. A pharmaceutical composition, comprising an effective amount of a compound of any one of claims 1-81 and a pharmaceutically acceptable diluent or carrier.

152. The pharmaceutical composition of claim 152, wherein said effective amount is effective to treat a vitamin D_3 associated state.

153. The pharmaceutical composition of claim 151, wherein said vitamin D_3 associated state is an ILT3-associated disorder.

154. The pharmaceutical composition of claim 152, wherein said vitamin D_3 associated state is a disorder characterized by an aberrant activity of a vitamin D_3-responsive cell.

155. The pharmaceutical composition of claim 152, wherein said vitamin D_3 associated state is bladder dysfunction.

156. A packaged formulation for use in the treatment of a vitamin D_3 associated state, comprising a pharmaceutical composition comprising a compound of any one of claims 1-81 and instructions for use in the treatment of a vitamin D_3 associated state.

157. The package formulation of claim 156, wherein said vitamin D_3 associated state is an ILT3-associated disorder.

158 The packaged formulation of claim 156, wherein said vitamin D_3 associated state is a disorder characterized by an aberrant activity of a vitamin D_3-responsive cell.

159. The packaged formulation of claim 156, wherein said vitamin D_3 associated state is bladder dysfunction.